REMARKS

The 35 U.S.C. §112 Rejections

Claims 5 and 10 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite for railing to point out and distinctly claim the subject matter which the applicant regards as the invention. This rejection is respectfully traversed.

Claim 10 has been cancelled herein. Therefore, the 35 U.S.C. §112, second paragraph rejection of claim 10 is ow moot. Claims 5 has been amended herein to proper Markush group format, as helpfully suggested by the Examiner. Therefore, the Applicants respectfully request that the rejection of claim 5 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 1 stands rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. This rejection is respectfully traversed.

The Examiner has rejected claim 1 because the claim, while enabling for the use of retinoids to upregulate CD-38 antigen as a cellular target and the use of monoclonal antibody conjugates specific for the upregulated CD38 antigen as a method of treating certain types of leukemia, does no enable the treatment of all

possible pathophysiological conditions, all possible antigenic stimulating antigens, nor all possible immunotoxins. Claim 1 has been amended herein to limit the claims to the treatment of acute myeloid leukemia, acute promyelocytic leukemia, lymphomas, and myelomas. The claim has also been amended to limit the claim to the upregulation of CD38 antigen by retinoids and to limit the immunotoxin to those specific for the CD38 antigen. The specification has shown that is effectively internalized upon immunotoxin binding. The Applicants maintain that as effective cytotoxins are well known to those of skill in the art, one skilled in the art could easily construct an effective immunotoxin from any antibody specific to CD38 and these toxins. Therefore, the Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 10 stands rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. This rejection is respectfully traversed.

Claim 10 has been cancelled herein. Therefore, the 35 U.S.C. §112, first paragraph rejection of claim 10 is now moot.

The 35 U.S.C. §102 Rejection

Claims 1 and 2 stand rejected under 35 U.S.C. §102(b) as anticipated by **Meridith** *et al.* (Clinical Cancer Research 2:1811, 1996). This rejection is respectfully traversed.

Meridith *et al.* upregulated the binding of anti-CEA and anti-TAG-72 antibodies by treating colorectal cancer patients with interferon. Claim 1 of the instant invention has been amended to specifically claim the upregulation of CD38 antigen by retinoids followed by treatment with immunotoxin specific for the CD38 antigen. **Meridith** *et al.* makes no reference to CD38 antigen, let alone the upregulation of CD38 by retinoids. Therefore, **Meridith** *et al.* fails to anticipate the instant invention. The Applicants respectfully request that the 35 U.S.C. §102(b) rejection of claims 1 and 2 over **Meridith** *et al.* be withdrawn.

The 35 U.S.C. §103 Rejections

Claims 1-3 and 7-11 stand rejected under 35 U.S.C. §103(a) as unpatentable over **Mehta** *et al.* (Proceeding of the American Association for Cancer Research, 38:88, 1997) in view of **Hirota** *et al.* (Cancer Research, 49:7106-7109, 1989). This rejection is respectfully traversed.

Mehta *et al.* teaches the killing of leukemia cell in culture through the upregulation of CD38 antigen expression followed by the administration of an anti-CD38 antibody-gelonin conjugate. **Hirota** *et al.* teaches the killing of squamous cells both in culture and in individuals through upregulation of the expression of the epidermal growth factor receptor (EGFR) with interferon alpha followed by treatment with an immunotoxin consisting of an anti-EGFR monoclonal antibody conjugated to gelonin. The Examiner argues that the effectiveness of the anti-EGFR-gelonin conjugate against squamous cell carcinoma. The applicant respectfully disagrees. CD38 and EGFR are entirely different proteins with different patterns of expression, internalization and antigenicities. CD38 and EGFR are upregulated by entirely different molecules, which differ in their range of activities and effects on normal cells. Thus, the fact that the augmentation of EGFR expression followed by immunotoxin treatment is effective against squamous cancer cells is effective against squamous cancer cells *in vivo* would not indicate whether retinoid enhancement of CD38 expression for immunotoxin targeting would also be effective *in vivo* because there are too many points at which the effectiveness of the two treatments could differ. Thus, the effectiveness of the instant invention *in vivo* could only be

determined by additional undue experimentation. Therefore, the Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 1-3 and 7-11 over **Mehta** *et al.* in view of **Hirota** *et al.* be withdrawn.

Claims 4-6 stand rejected under 35 U.S.C. §103(a) as unpatentable over **Mehta** *et al.* (Proceeding of the American Association for Cancer Research, 38:88, 1997) in view of **Hirota** *et al.* (Cancer Research, 49:7106-7109, 1989) as applied to claims 1-3 and 7-11, in further view of **Mehta** *et al.* (Proceeding of the American Association for Cancer Research, 35:92, 1994). This rejection is respectfully traversed.

As argued above, the combination of **Mehta (1997)** and **Hirota** do not render obvious the instant invention because of the considerable differences in the cell surface targets and molecules used to augment expression. While **Mehta (1994)** uses some of the same specific retinoid as the instant to augment the expression of CD38, **Mehta (1994)** fails to overcome the other deficiencies in the combination **Mehta (1997)** and **Hirota** with regard to the instant invention. Therefore, the Applicants respectfully request that the 35 U.S.C. §103(a) rejection of claims 1-

3 and 7-11 over **Mehta** *et al.* in view of **Hirota** *et al.* in further view of **Mehta** *et al.* be withdrawn.

This is intended to be a complete response to the Office Action mailed March 2, 2000. Applicants submit that the pending claims are in condition for allowance. If any issues remain, please telephone the attorney of record for immediate resolution.

Respectfully submitted,

DATE: 8/31/00

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